1212/10109293/MBW. Reconsideration of the application in view of the following amendments and remarks is respectfully requested.

I. AMENDMENT

Please make the following amendments:

In the Claims:

Please cancel claims 1-25, 36, 41, 45-47, and 51-60, and amend the claims as follows:

26. (Amended) A method for enhancing or inducing immunity to a viral infection comprising expressing a serpin or a serpin mimetic [granzyme inhibitor] in a [the] cytotoxic T-lymphocyte [T-lymphocytes] of a subject by introducing an expression construct comprising a DNA segment encoding the serpin or serpin mimetic [granzyme inhibitor] under the control of a promoter active in the cytotoxic T-lymphocyte.

A1

30. (Amended) A method for enhancing or inducing immunity to a virus comprising:

a) obtaining a cytotoxic T-lymphocyte that comprises an expression vector that comprises a DNA segment encoding a serpin or a serpin mimetic [granzyme inhibitor] under the control of a promoter active in the cytotoxic T-lymphocyte; and

b) administering the cytotoxic T-lymphocyte to a subject in need thereof.

A2

34. (Amended) The method of claim 30, wherein the serpin or serpin mimetic [granzyme inhibitor] inhibits granzyme activity, inhibits granzyme transcription, inhibits granzyme translation, increases granzyme degradation, or destabilizes granzyme.

A3

A3 cont

35. (Amended) The method of claim 30, wherein the serpin or serpin mimetic [granzyme inhibitor] inhibits granzyme function.

37. (Amended) The method of claim 30 [36], wherein the serpin or serpin mimetic [polypeptide] is a serpin.

38. (Amended) The method of claim 30 [37], wherein the serpin is SPI6, PI9, PI-6, monocyte neutrophil elastase inhibitor (MNEI), PI-8, plasminogen activator inhibitor 2 (PAI-2).

A4

39. (Amended) The method of claim 38 [37], wherein the serpin is SPI6.

40. (Amended) The method of claim 38 [37], wherein the serpin is PI9.

42. (Amended) The method of claim 30 [41], wherein the virus is HIV, LCMV, HCV, HTLV-1, HTLV-2, EBV, HBV, human cytomegatovirus, Herpes simplex 1, Herpes simplex 2, hepatitis G, enterovirus, dengue fever virus, or rabies virus.

A5

Please add the following new claims:

61. (New) The method of claim 26, wherein the expression construct is a viral expression construct.

A6

62. (New) The method of claim 61, wherein the viral expression construct is selected from the group consisting of a retrovirus, an adenovirus, an adeno-associated virus, a herpesvirus, a polyoma virus, and a vaccinia virus.

63. (New) The method of claim 62, wherein the expression construct comprises a retroviral vector.

64. (New) The method of claim 26, wherein the serpin or serpin mimetic inhibits granzyme activity, inhibits granzyme transcription, inhibits granzyme translation, increases granzyme degradation, or destabilizes granzyme.

AL cont

65. (New) The method of claim 26, wherein the serpin or serpin mimetic inhibits granzyme function.

66. (New) The method of claim 26, wherein the serpin or serpin mimetic is PI9 or a PI9 mimetic.

67. (New) The method of claim 26, wherein the serpin or serpin mimetic is a serpin.

68. (New) The method of claim 67, wherein the serpin is SPI6, PI9, PI-6, monocyte neutrophil elastase inhibitor (MNEI), PI-8, plasminogen activator inhibitor 2 (PAI-2).

69. (New) The method of claim 68, wherein the serpin is SPI6.

70. (New) The method of claim 68, wherein the serpin is PI9.

71. (New) The method of claim 26, wherein the virus is HIV, LCMV, HCV, HTLV-1, HTLV-2, EBV, HBV, human cytomegatovirus, Herpes simplex 1, Herpes simplex 2, hepatitis G, enterovirus, dengue fever virus, or rabies virus.

A6 cont

72. (New) The method of claim 69, wherein the virus is HIV.

73. (New) The method of claim 69, wherein the virus is LCMV.

74. (New) The method of claim 30, wherein the serpin or serpin mimetic is PI9 or a PI9 mimetic.

II. RESPONSE TO OFFICE ACTION

A. Status of the Claims

The Action acknowledges Applicants' election, without traverse, of the invention of group II (*i.e.*, claims 26-50). Consequently, claims 1-25 and 51-60 have been withdrawn from consideration as being drawn to a nonelected invention, and are canceled in the Amendment submitted herein. Therefore, claim 26-50 were pending at the time of the Action. Claims 26, 30, 34-35, 37-40, and 42 have been amended in the Amendment contained herein. Claims 1-25, 36, 41, 45-47, and 51-60 have been canceled. Claims 61-74 have been added. Therefore, claims 26-36, 37- 40, 42- 44, 48-50, and 61-74 are presently pending. A copy of the amended claims with editing indicia is attached as Appendix A. A clean copy of the presently pending claims is attached as Appendix B.

B. The Rejection of Claims 26-50 Under the Written Description Requirement of 35 U.S.C. §112, First Paragraph, is Overcome

The Action rejects claim 26-50 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the Specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. In particular, the Examiner asserts that the Specification does not provide sufficient written description support for the claimed genus of granzyme inhibitors. The Examiner also asserts that the Specification does not provide sufficient teaching regarding the subgenus of modulators and inhibitors of granzyme activity, including inhibitors of granzyme transcription and translation. Applicants respectfully traverse this rejection.

Present independent claims 26 and 30 recite "serpin or serpin mimetic." Without conceding that the Specification does not provide sufficient written description for the claims as originally filed, Applicants assert that the Specification provides sufficient written description support for the claimed genus of "serpin or serpin mimetic," and any subgenuses of this genus. The Examiner objected to the lack of a representative number of species of members of the claimed genus of "granzyme inhibitor." The Specification clearly discloses a representative number of species of the genus "serpin and serpin mimetics." See Specification, page 4, lines 20-26; page 5, lines 21-23; page 15, lines 15-16; Page 15, line 21 through page 16, line 4; Page 19, lines 12-14; Page 37, lines 22-24. In particular, a review article pertaining to serpins is cited on page 4, line 21 of the Specification. Examples of particular serpins useful in the context of the invention are cited in the Specification, and include SPI6, PI9, PI-6, monocyte neutrophil elastase inhibitor (MNEI), PI-8, and plasminogen activator inhibitor (PAI-2). Specification, page 6, lines 21-24. One of skill in the art would be familiar with the substantial amount of information that is available pertaining to serpins and the numerous types of serpins that have been identified.

A detailed description of serpin mimetics is also provided in the Specification. Specification, page 6, line 26 to page 7, line 23. In addition, each of the Examples delineated in the Specification provide substantial information pertaining to serpins, in particular SPI6 and PI9, in the context of the present invention. Specification, Examples 1-13 (page 67, line 22 through page 89, line 4). Therefore, Applicants assert that the Examiner's concerns regarding lack of a representative number of members of the genus have been overcome.

Applicants also understand that the Examiner's concerns regarding lack of identifying characteristics of the subgenuses have been overcome. As discussed above, the Specification

provides substantial information pertaining to serpins and serpin mimetics, and one of ordinary skill in the art would be familiar with the substantial information that is known about various types of serpins. For example, the Specification provides substantial information pertaining to PI9 and PI9 mimetics. See Specification, page 4, lines 23-26; page 6, lines 21-24; page 6, line 26 through page 7, line 23; page 15, lines 16-17; page 19, lines 12-14; page 27, lines 22-24; and Example 13 (page 88, line 30 through page 89, line 4). Substantial information pertaining to PI9 mimetics is provided in the Specification. Specification, page 6 line 26 through page 7, line 23. In addition, Example 13 provides information pertaining to the use of PI9 as an agent to increase the potency of human cytolytic lymphocytes. Specification, page 88 line 30 through page 89, line 4.

The objective standard for determining compliance with the written description requirement is whether "the description clearly allow[s] persons of ordinary skill in the art to recognize that he or she invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 U.S.P.Q.2d 1614, 1618 (Fed. Cir. 1989). The Federal Circuit has also noted that an Applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 U.S.P.Q.2d 1961, 1966 (Fed. Cir. 1997).

Applicants assert that the Specification of the instant application clearly allows one of skill in the art to recognize that Applicants invented what is claimed. In particular, the Specification provides substantial information pertaining to serpins and serpin mimetics. The Specification also teaches a large number of representative members of the genus of serpins, and provides substantial information pertaining to members of the genus of serpins such as PI9 and

subgenuses such as mimetics of PI9. One of ordinary skill in the art would also be familiar with the vast amount of information known in the art pertaining to serpins. Additionally, in view of the information provided in the Specification pertaining to mimetics, one of skill in the art would be able to understand how to make and use the claimed invention with regard to serpin mimetics and mimetics of PI9. This is particularly true in view of the substantial information provided by the Examples in the Specification discussed *supra*.

Therefore, the written description rejections under 35 U.S.C. §112, first paragraph, should be withdrawn.

C. The Rejection of Claims 26-50 Under the Enablement Requirement 35 U.S.C. §112, First Paragraph, is Overcome

Claims 26-50 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the Specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Examiner's concerns appear to be focused on three main areas: (1) the scope of the claims; (2) the alleged unpredictability of the art of gene therapy and CTL therapy; and (3) a concern for lack of applicability of the results disclosed in the specification to HIV disease. Applicants respectfully traverse each of these rejections.

1. The Claims as Written are Sufficiently Described in the Specification to Meet the Enablement Requirement

The Examiner first addresses concerns regarding the breadth of the claims. More particularly, the Examiner notes that the claimed invention is drawn to a method of inducing

immunity or enhancing immunity in a subject with any disease with any granzyme inhibitor. As a result, the Examiner asserts that practicing the invention would require undue experimentation.

Without conceding that the Specification is not enabling for the claims as originally written, Applicants draw the Examiner's attention to the presently pending claims. The claims encompass methods for enhancing or inducing immunity to a viral infection that involves expressing a serpin or a serpin mimetic. As discussed and cited above, the Specification provides a substantial amount of information pertaining to serpins and serpin mimetics, as well as PI9 and PI9 mimetics.

The Specification also provides a substantial amount of information pertaining to enhancing or inducing immunity to a viral infection. A discussion pertaining to the epidemiology of viral infection is provided on page 2, lines 17-23 of the Specification. The role of CTLs in viral infection is discussed in the Specification on page 3, line 1 through page 5, line 17; page 13, line 20 through page 14, line 24; and page 14, line 27 through page 16, line 4. Application of the invention to the treatment of viral disease is discussed in the Specification on page 8, lines 11-15. The inventors discuss that they have demonstrated the ability to use granzyme B inhibitors to successfully eliminate virus, as shown using the transgenic mouse model of LCMV infection. Specification, page 14, lines 6-17. Application of the methods disclosed in the Specification to treatment of HIV disease is discussed on page 10, lines 6-19. Animal models of viral infection, including a discussion of techniques such as CTL assays, are discussed in the Specification on page 50, line 10 through page 52, line 12 of the Specification. Human treatment protocols of viral infection are addressed in the Specification on page 63, line 28 through page 67, line 7.

The working examples address application of the invention to treatment of viral disease. In particular, the working examples demonstrate the effect of SPI6 on the LCMV-infected mouse. Example 1 provides general information pertaining to LCMV infection in mice and CTL assays. Specification, page 67, line 22 through page 69, line 19. Example 2 demonstrates that mouse Serpin SPI6 protects cells from apoptosis by granzyme B. Specification, page 69, line 24 through page 71, line 21. Example 7 discusses results pertaining to the clonal exhaustion induced by LCMV infection in mice. Specification, page 78, line 15 through page 79, line 2. Example 12 demonstrates the protective effect of SPI6 on CTLs in LCMV infection, and demonstrates that granzyme B is involved in the development of memory cells. Specification, page 84, line 10 through page 88, line 25.

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. See *In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988); *United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 U.S.P.Q.2d 1217, 1223 (Fed. Cir. 1988). Based on the disclosure in the Specification, particularly those sections pertaining to treatment of viral disease, serpins, and serpin mimetics, one of ordinary skill in the art would be able to make and/or use the claimed invention without undue experimentation.

It is possible that a certain amount of minimal experimentation may be required to practice the claimed invention. However, even if some experimentation may be required, it is certainly not undue experimentation. See *In re Angstadt*, 537 F.2d 498, 504, 190 U.S.P.Q. 214, 219 (C.C.P.A. 1976) (The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue).

2. The Art of Gene Therapy and Cell Therapy are not so Unpredictable as to Preclude Enablement

Next, the Examiner states the opinion that the Specification is not enabling because the art of gene therapy and cell therapy using CTLs is unpredictable, and the Specification does not provide any guidance as to how to address the issues of unpredictability in the art. In support of this position, the Examiner cites Romano *et al.* (Stem Cells, 18: 19-39, 2000).

The Examiner's position concerning gene therapy and cell therapy using CTLS as being inoperable is simply not the case. The abstract of Romano *et al.* states the following:

> "Over the last decade, more than 300 phase I and phase II gene-based clinical trials have been conducted worldwide for the treatment of cancer and monogenic disorders. Lately, these trials have been extended to the treatment of AIDS and, to a less extent, cardiovascular diseases. There are 27 currently active gene therapy protocols for the treatment of HIV-1 infection in the USA. Preclinical studies are in progress to evaluate the possibility of increasing the number of gene therapy clinical trials for cardiomyopathies, and of beginning new gene therapy programs for neurologic illnesses, autoimmune diseases, allergies, regeneration of tissues, and to implement procedures of allogeneic tissues or cell transplantation. In addition, gene transfer technology has allowed for the development of innovative vaccine design, known as genetic immunization. This technique has already been applied to AIDS vaccine programs in the USA. These programs aim to confer protective immunity against HIV-1 transmission to individuals who are at risk of infection."

Romano *et al.* was published 3 years ago, and even at that time, gene therapy clinical trials were not uncommon. Romano *et al.* also indicates that gene therapy as applied to HIV disease was gaining rapid ground.

Even though gene therapy and cell therapy using CTLs may not be commonplace today from a clinical standpoint, they most certainly are sufficiently enabling for patenting. Even the PTO must admit that the number of patents that encompass these types of therapies is considerable.

While each case is taken on its own merits, the PTO cannot cling to the notion that gene therapy or CTL therapy is *per se* lacking in enablement. It is critical to make the distinction between the necessary showing under 35 U.S.C. §112, and that needed to establish clinical efficacy. Controlling precedent makes it clear that even those therapies ultimately without use in the clinic are of value, and therefore may be patented. *In re Krimmel*, 130 U.S.P.Q. 215, 219 (C.C.P.A. 1961).

3. LCMV Infection in the Mouse is a Well-known and Established Model for Viral Infection in Humans, Including HIV Infection

The Examiner holds to the view that the Specification is not sufficiently enabling because it "does not teach how to induce immunity in an HIV infected subject or any subject with any disease by the claimed method." Office Action, page 4, paragraph 1. According to the Examiner, "it is uncertain whether there would be a therapeutic effect when the studies obtained in a mouse model or another animals [sic] model is extended to a human subject." Office Action, page 6, first paragraph. The Examiner also claims that the LCMV-infected mouse disclosed in the working examples is "not a natural animal model because there is no issue of gene delivery to cells since the mouse has the transgene in all of its cells." Office Action, page 6, second paragraph. Therefore, the Examiner concludes that one of ordinary skill in the art would not be able to make and/or use the invention, particularly with regard to the treatment of viral disease such as HIV, without undue experimentation.

Applicants assert that one of ordinary skill in the art would readily recognize that the LCMV mouse is a well-known and well-established model for HIV infection in humans, and that in view of the disclosure in the Specification, one of ordinary skill in the art would be able to

make and/or use the invention without undue experimentation. In support of this position, Applicants herein provide the declaration of Raymond M. Welsh, Ph.D., Professor in the Department of Pathology at the University of Massachusetts Medical Center (Worcester, MA) (Appendix C).

Dr. Welsh is a skilled virologist who understands the immunology of viral infections. Evidence of Dr. Welsh's expertise in viral immunology is provided on page 1, paragraph 2 and page 2, paragraph 3 of Appendix C. Dr. Welsh declares that "[a] skilled virologist with an ordinary understanding of viral immunology would have recognized, at the time the above-referenced application was filed, that LCMV infection in mice is a model for determining the usefulness of the claimed invention for treating other viral diseases, including HIV." Appendix C, page 3, paragraph 7. He also declares that "a skilled virologist with an ordinary understanding of viral immunology would have understood, at the time the above-referenced application was filed, that LCMV infection in mice was a model for HIV infection in humans." Appendix C, page 3, paragraph 7.

Dr. Welsh notes that his position with respect to the accepted nature of the LCMV mouse model is supported by literature that would be familiar to one having an ordinary understanding of viral immunology. Appendix C, page 3, paragraph 8. The articles cited by Dr. Welsh include Zinkernagel, Vaccine 20:1913-1917, 2002 (Appendix C, Exhibit 1), Klenerman and Zinkernagel, Immunological Reviews, 159:5-16, 1997 (Appendix C, Exhibit 2), Borrow *et al.*, J. Virology, 69:1059-1070, 1995 (Appendix C, Exhibit 3), Ciurea *et al.*, Proc. Natl. Acad. Sci. USA, 96:11964-11969, 1999 (Appendix C, Exhibit 4), and Odermatt *et al.*, Proc. Natl. Acad. Sci. USA, 88:8252-8256, 1991 (Appendix C, Exhibit 5). In addition, Dr. Welsh has reviewed the Specification, and has identified specific sections of the Specification that directly pertain to

LCMV infection and HIV. See Appendix C, page 7, paragraph 10. Based on his review of the cited references and sections of the Specification, Dr. Welsh declares that "the present claims contain subject matter which was described in the specification in such a way as to enable a skilled virologist with an ordinary understanding of viral immunology to make and/or use the invention."

Further, Dr. Welsh concludes that "no undue experimentation would be required for a skilled virologist with an ordinary understanding of viral immunology to make and/or use the claimed invention of the above-referenced application as it is currently claimed." Appendix C, page 8, paragraph 12.

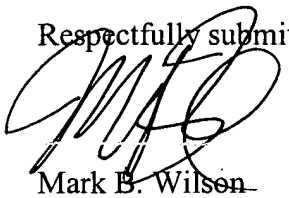
As discussed *supra*, the test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. See *In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988); *United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 U.S.P.Q.2d 1217, 1223 (Fed. Cir. 1988). Dr. Welsh's declaration clearly indicates that one of ordinary skill in the art would have understood, at the time the above-referenced application was filed, that the Specification teaches inducing or enhancing immunity in a subject against HIV, and that the claimed invention could be made and/or used without any undue experimentation.

Applicants assert that in view of the above, they have met their burden of presenting persuasive arguments, supported by suitable proof, that one skilled in the art would be able to make and use the claimed invention using the application as a guide. *In re Brandstadter*, 484 F.2d 1395, 1406-07, 179 U.S.P.Q. 286, 294 (C.C.P.A. 1973). Accordingly, the rejections under 35 U.S.C. 112, first paragraph, should be withdrawn.

D. Conclusion

In view of the foregoing, it is believed that all claims are in condition for allowance, and an early notification to that effect is earnestly solicited. The Examiner is invited to contact the undersigned at (512) 536-3035 with any questions, comments, or suggestions relating to the referenced patent application.

Respectfully submitted,



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